FEATURE – SARS-CoV-2

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TEXT:

Structural and computational biology play key roles in elucidating molecular mechanisms of disease phenotypes and in driving drug discovery. This is exemplified by the current fast-paced efforts to respond to the COVID-19 pandemic. To aid these endeavors, the University of Bristol set up a COVID Emergency group (UNCOVER), coordinated by Bristol clinician Adam Finn, that initiated multi-disciplinary collaborations among virologists, chemists, physicians, pharmacologists and others to accelerate our understanding of COVID-19 and to design tailored treatments urgently needed to overcome the crisis. In our contribution, we discovered a druggable pocket in the SARS-CoV-2 spike (S) glycoprotein, the viral component that mediates interaction with the cellular ACE2 receptor and that is essential for infection [1]. In our cryo-EM structure of S, this pocket was occupied by linoleic acid (LA), an essential poly-unsaturated free fatty acid (FFA). LA stabilized S in a locked conformation that is incompatible with ACE2 binding and is thus considered 'non-infective'. Intriguingly, LA synergizes with remdesivir, the first drug approved for COVID-19 treatment, to block viral replication in cells [1]. Our discovery has actionable implications: the data suggest that LA could act as a prophylactic antiviral. Intriguingly, sera of COVID-19 patients have decreased levels of FFAs, including LA [2]; therefore LA

supplementation may be beneficial. Small molecules binding the FFA-binding pocket (LA mimics) have potential as future antivirals as they might lock S in a non-infective conformation. Finally, t~~T~~he body metabolizes LA to eicosanoids, including prostaglandin, key molecules in immune modulation. In addition, LA-based phospholipids maintain fluidity of cell membranes and surface tension in the lung. While more research is required to decipher the interplay of FFAs, SARS-CoV-2 and COVID-19 pathology~~Thus~~, targeting the LA metabolic axis could help prevent rampant inflammatory responses in severe cases of COVID-19 and reduce respiratory distress and the risk of pneumonia in patients. ~~Finally, LA mimics have potential as future small-molecule antivirals as they might lock S in a non-infective conformation. While more research is required to decipher the interplay of FFA, SARS-CoV-2 and COVID-19 pathology, our research provides avenues to explore in the fight of COVID-19.~~

Commented [AS1]: Moved up, because I think the transition to LA supplementation works very well, while the pocket-binding drugs cover another aspect of the work.

Commented [CB2R1]: I agree, it works well this way.

References:

1. Toelzer, C. *et al.* Free fatty acid binding pocket in the locked structure of SARS-CoV-2 spike protein. *Science*, DOI: 10.1126/science.abd3255 (2020).

2. B. Shen *et al.*, Proteomic and Metabolomic Characterization of COVID-19 Patient Sera. *Cell* **182**, 59-72 (2020).

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